

Abstract

Overexpression of the hypoxia inducible factor 1 (HIF-1) and HIF-2 transcription factors and the consequent upregulation of hypoxia inducible mRNAs is a feature of many human cancers and may be unrelated to tissue hypoxia. Thus, the VHL (von Hippel-Lindau) tumour suppressor gene (TSG) regulates HIF-1 and HIF-2 expression in normoxia by targeting the alpha subunits for ubiquitination and proteolysis. Inactivation of the VHL TSG in VHL tumours and in sporadic clear cell renal cell carcinoma (RCC) results in overexpression of HIF-1 and HIF-2. However, RCC without VHL inactivation may demonstrate HIF upregulation, suggesting that VHL independent pathways for HIF activation also exist. In RCC, three candidate HIF activating genes exist-FIH-1 (factor inhibiting HIF), SDHB, and FH-which may be dependent or independent of VHL inactivation. To investigate FIH-1, SDHB, and FH for somatic mutations in sporadic RCC. Gene mutation was analysed in primary RCCs (clear cell RCCs, papillary RCCs, and oncocytomas) and RCC cell lines. SDHB mutation analysis was performed by denaturing high performance liquid chromatography followed by direct sequencing of aberrant PCR products. FH and FIH-1 mutation analysis were performed by single stranded conformational polymorphism and direct sequencing of PCR products. No mutations were identified in the three genes investigated. There was no evidence to suggest that somatic mutations occur in the FH, FIH-1, or SDHB TSGs in sporadic RCCs.